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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,509	07/23/2001	Roger Nitsch	P63142US1	9340

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EXAMINER	
CHERNYSHEV, OLGA N	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 05/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,509	NITSCH ET AL.	
	Examiner	Art Unit	
	Olga N. Chernyshev	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *23-36* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 April 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/23/1*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II in the reply filed on March 30, 2006 is acknowledged. The traversal is on the ground(s) that "restriction would result in dividing a proper generic claim". Applicant's argument has been fully considered, found to be persuasive and Groups I and II have been rejoined.

Claims 23-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on March 30, 2006.

Claims 1-22 are under examination in the instant office action.

Sequence compliance

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821 (a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825. Specifically, no sequence identification has been provided for the nucleic acid sequences presented in Figure 3 of the instant specification. In case these sequences are new, Applicant needs to provide a substitute computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences that are present in the instant application and encompassed by these rules, a substitute paper copy of that "Sequence Listing", an amendment directing the entry of that paper copy into the specification, and a statement that the content of the paper and computer

readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). The instant specification will also need to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. See M.P.E.P. 2422.04.

3. The text of the instant specification is not in compliance with the requirements for Sequence Identifiers, see pages 13, 16, 32 and 37, for example (see MPEP 2422.03). The appropriate format for sequence identifiers is SEQ ID NO: X, wherein "X" is the sequence number. Appropriate correction is required.

Drawings

4. The figures of the instant application are presented on separate pages or in separate panels. 37 C.F.R. § 1.84(u) (1) states that in cases when figures present partial views of a drawing, which are intended to form one complete view, whether contained on one or several sheets, the figures must be identified by the same number followed by a capital letter. For example, the two panels of Figure 2 in the instant specification should be renumbered "Figure 2A" – "Figure 2B" rather than "Figure 2". Applicant is reminded that once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84(u) (1), the specification should be amended to change the Brief Description of the Drawings and the rest of the specification to refer to each Figure accordingly. If, for example, Figure 2 is divided into Figures 2A-2B, then the Brief Description and all the references to this figure in the specification must refer to this Figure in the same manner.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 17-22 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. The term "increase" in claim 1 is a relative term, which renders the claim indefinite. The term "increase" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Including the point of reference within the claim would obviate this ground of rejection.

10. Claim 1 recites the limitation "said cerebrospinal fluid". There is insufficient antecedent basis for this limitation within the claim.

11. Claim 1 is further vague and ambiguous for recitation "increase of a level or a varied activity". The metes and bounds of the recitation cannot be determined from the claim or the instant specification.

12. Claims 1 and 12 are vague and indefinite for reciting "diagnosing or prognosing" as limitations. Because the instant specification, as filed, fails to define diagnosis and prognosis, these two terms appear to encompass the same thing. Clarification is required.

13. Claim 5 is vague and ambiguous with respect to recitation "wherein said subject is a human". According to the knowledge in the art, Alzheimer's disease is only described within human population; therefore, claim 5 appears to be a duplicate or claim 1 for encompassing essentially the same subject matter.

14. Claim 6 is indefinite for recitation "translation product [...] is determined in its monomer form". The metes and bounds of the recitation are not clear. It is advised that the claim is rewritten to better express claimed subject matter.

15. Claim 9 is indefinite because it is not obvious and cannot be determined from the claim if "series of samples" encompasses the same type of samples or samples of different origin or both.

16. Claims 10 and 11 are vague because it is not clear what treatment is intended by the claims. Is it a treatment of Alzheimer's disease, or a different treatment?

17. Claim 12 is indefinite for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the step that leads to the diagnosis or prognosis of Alzheimer's disease. It appears that determination of absence of a

polymorphism in a cystatin C gene cannot lead to diagnosis of Alzheimer's disease. Clarification is required.

18. Claim 13 does not make sense. Applicant is advised to rewrite the claim to better express the claimed subject matter.

19. Claims 2-4, 7-8 and 14-16 are indefinite for being dependent from indefinite claims.

20. Claims 17-22 provide for the use of a kit, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

21. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

22. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-16 are directed to methods for diagnosing, prognosing, determination of a risk, monitoring the progression and evaluating a treatment of Alzheimer's disease (AD) in a subject by comparing levels or an activity of cystatin C gene or its product in samples obtained from the subject with AD to corresponding control value. However, the instant specification fails to provide enough guidance for one skilled in the art on how to practice the instant methods,

thereby requiring undue experimentation to discover how to use Applicant's invention, as currently claimed.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The instant invention is based on the results of evaluation of cystatin C protein amount in CSF samples obtained from patients with a clinical diagnosis of probable AD (top at page 30 of the instant specification) and further comparison of the data to the corresponding levels of cystatin C in CSF samples obtained from patients suffering from other clinical conditions as well as to healthy controls (see Tables 1 and 2 and text at pages 30-39). The art recognizes that cystatin C protein (also known as γ-trace protein) is present in detectable amounts in CSF and plasma under normal and pathological conditions (see articles by Lofberg et al., 1980, IDS of 07/23/2001; Davidsson et al., 1997, J. Neural Transm, Vol. 104, pp.711-20; Grubb et al, 1985, Scand. J. Clin. Lab. Invest., 177, pp.7-13). Specifically, Lofberg et al. disclose that concentration of cystatin C protein in CSF and plasma depends from multiple factors, such as age and clinical conditions (see abstract, Tables 1 and 2, pages 162-165 and also page 5 of the instant specification). Article by Grubb et al. further confirms a marked variation of CSF concentration of cystatin C protein with age (see p.8 and Fig. 1). Furthermore, Lofberg et al. specifically recite conditions, in which concentration of cystatin C protein in CSF and plasma is increased as

compared to normal control (see Tables 1-2). It is not recognized in the art that increased level or activity of cystatin C protein is specifically associated with Alzheimer's disease. Moreover, at the time of invention, a specific biological role or activity of cystatin C protein, especially with respect to AD etiology, appears to be unknown.

Thus, the state of the art can be characterized as (1) recognizing that CSF contains detectable amounts of cystatin C protein (γ-trace protein), (2) that concentration of cystatin C protein varies significantly with age and during certain pathological conditions, and (3) that increased levels of cystatin C protein are characteristic of multiple unrelated neurological and infectious diseases.

While the skill level in the art is high, the level of predictability is low. The art clearly discloses that levels of cystatin C protein in CSF are elevated during development and certain pathological conditions. The instant specification, as originally filed, presents working examples, which pertain to the analysis of CSF concentration of cystatin C in patients with probable AD as compared to other clinical conditions and healthy control. Two sets of the results show (1) not significantly elevated concentration of cystatin C protein in AD samples (Table 1, 11.25 ± 4.43 μg/ml) and (2) significantly higher concentration of cystatin C in AD (Table 2, 11.0 ± 1.20 μg/ml) as compared to healthy control and to other diseases. It is noted that cysteine C concentration was also increased in samples marked "Epilepsy", "Psychosis" and "Non-AD neurodegeneration" *vs.* "healthy control". Based on the obtained data, Applicant proposes a general method of diagnosis of AD, wherein increased level of cystatin C protein in a sample obtained from a patient is diagnostic of AD. However, the standard of an enabling disclosure is not the ability to make and test if the invention worked but one of the ability to make and use

with a reasonable expectation of success. While it is not necessary that Applicant understands or discloses the mechanism by which the invention functions, in this case, in the absence of such an understanding, no extrapolation can be made of the limited results of analysis of cysteine C amounts in CSF samples of not-confirmed AD cases to methods of diagnosis, prognosis, monitoring etc. of AD in view of (1) the art recognition that elevated levels of cystatin C appear to be associated with many pathological conditions, and (2) Applicant's own data, in which cystatin C is elevated under other disease conditions.

Furthermore, with respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the enablement scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification (see MPEP 2111 [R-1], which states that claims must be given their broadest reasonable interpretation

"During patent examination, the pending claims must be "given *>their< broadest reasonable interpretation consistent with the specification." *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). Applicant always has the opportunity to amend the claims during prosecution, and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550- 51 (CCPA 1969)".

As such, by broadest reasonable interpretation, the claimed methods encompass diagnosis, prognosis, determination of risk of development of AD by determination of level of cystatin C protein in any sample obtained from a subject, such samples include body fluid

samples (saliva, urine, sweat, for example) and any tissue samples. The instant specification fails to present any evidence that any sample obtained from a subject contains cystatin C protein and is suitable for determination of level of cystatin C protein for diagnostic purposes. It would require a significant amount of undue experimentation on part of a skilled practitioner to discover which samples can be used to successfully practice the instant methods, as currently claimed.

Applicant's invention is predicated on the finding that levels of cystatin C protein are elevated in CSF samples of patients diagnosed with probable Alzheimer's disease. Applicant further extrapolates this result into a method for diagnosing, prognosing, determination of a risk, monitoring the progression and evaluating a treatment of Alzheimer's disease in a subject by comparing levels or activity of cystatin C gene or its product in biological samples. Accordingly, it would appear that Applicant provides a single finding (the finding), and then presents an invitation to experiment and determine what samples are suitable for diagnostic analysis, what activity of cystatin C protein is specifically associated with AD, and then to assay for changes in concentration of cystatin C during course of AD, treatment of AD, as well as to discover the connection between levels of cystatin C and risk of development of AD.

Finally, with respect to determination of a polymorphic variant of a cystatin C gene as a marker for AD, the instant specification fails to provide any evidence or sound scientific reasoning that determination of "a presence or absence of a polymorphism in cystatin C gene" could lead to diagnosis, prognosis or determination of risk of development of AD. It is well known in the art of molecular biology that essentially any one of many different genes and proteins found within a particular species of organism will vary in form between different

individuals of the species. It is well accepted in the art that almost every gene in the human genome, for example, can be found in more than one allelic form. Since the instant specification fails to disclose how any polymorphism found within a cystatin C gene be diagnostic of risk to develop AD, for example, in order to practice the claimed invention, one skilled in the art would have to first engage in a substantial amount of undue experimentation.

A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentec, Inc, v. Novo Nordisk*, 42 USPQ 2d 100,(CAFC 1997), the court held that:

"[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one can not follow the guidance presented therein and practice the claimed method without first making a substantial inventive contribution.

Double Patenting

23. Applicant is advised that should claim 1 be found allowable, claim 16 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

24. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (571) 272-0870. The examiner can normally be reached on 8:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Olga N. Chernyshev, Ph.D.

Primary Examiner
Art Unit 1649

May 1, 2006